REMARKS

This application is a continuation of Application No. 09/856,352, filed October 17, 2001. Application No. 09/856,352 is the national phase of PCT International Application No. PCT/1899/00284, filed November 22, 1999 under 35 USC §371.

In U.S. Patent Application No. 09/856,352, several rejections were imposed in the application. Claims 7-11 were rejected under 35 USC §102(b) as allegedly be anticipated by RUPREHT et al. Claims 12-13 were rejected under 35 USC §103(a) as allegedly being obvious in view of RUPREHT et al. Claims 7-13 were rejected under 35 USC §103(a) as allegedly being unpatentable over ENZ in view of OSHIRO et al. Upon reviewing these publications, applicants believe that neither of these publications, alone or in combination, disclose or suggest the claimed invention.

This patent application relates to the use of effectors of the central cholinergic nervous system (e.g. cholinesterase-inhibitors) for the production of a preparation to treat non-anticholinergic delirium.

A state of delirium can be caused by a great number of predisposing and precipitating factors (Inouye SK. Delirium in Hospitalized Older Patients. Clin. Geriatr. Med. 1988;14:745-764). Only a few studies have systematically described the different causes of delirium (Francis J, et al. A Prospective Study of Delirium in Hospitalized Elderly. JAMA 1990;263:1097-101). Indeed,

the latter study demonstrated that 30% of deliria were at least partially caused by drug toxicity. One type of drug that might induce a state of delirium are anticholinergically acting drugs. Inouye (1988) teaches that the use of anticholinergics increases the risk of suffering from delirium to 4.5 - 11.7 fold.

In the present application, anticholinergic delirium is defined as a delirium which occurs when anticholinergically acting substances are administered to an individual. Anticholinergic delirium is one manifestation of the "central anticholinergic syndrome", a term used in anaesthesiology. The term includes patients in a comatose state from anticholinergic intoxication.

Deliria can be classified into types of categories, anticholinergically induced deliria or non-anticholinergically induced deliria.

Non-anticholinergic deliria is caused by fluid or electrolyte abnormalities, due to metabolic disorders, low perfusion, infection, hypoxaemia, hypoxia, acid-base disturbances, or intoxication with non-anticholinergically acting drugs like benzodiazepines or lithium (Lipowski, ZJ. Delirium (Acute Confusional States). JAMA 1987;258:1789-92; Flacker JM & Marcantonio ER. Delirium in the Elderly. Drugs & Aging 1998;13:119-30; O'Keeffe ST, Chonchubhair AN. Postoperative Delirium in the Elderly. Br J Anaesth 1994;73: 673-87).

Anticholinergics are used nowadays with low frequency because of their delirogenic potency. Therefore, modern studies

show no association between anticholinergics and delirium (Marcantonio ER. et al, The Relationship of Postoperative Delirium With Psychoactive Medications. JAMA 1994;272: 1518-22). While older surveys teach that drugs with anticholinergic activity are likely to induce deliria (Lipowski ZJ, 1987: p.1790), the Lipowski publication also describes the pharmacotherapy of delirium with neuroleptics like haloperidol.

Lipowski states that "In severe anticholinergic intoxication, physostigmine salicylate, 1 to 2 mg, should be given slowly intravenously or intramuscularly". Flacker et al. also teach that anticholinergic drugs and toxins can be a cause of delirium" (p.123). On page 125, they write that "In particular,... an anticholinergic medication should be suspected as one of the causes for delirium." Flacker et al. recommend that "In severe delirium, attributable to anticholinergic agents, physostigmine may be tried, ..." (p. 126, last paragraph).

Thus, it is that a subtype of delirium, namely anti-cholinergically-induced delirium, that may be treated by cholinomimetic agents like physostigmine. As a consequence, one might even consider the second generation of acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) could also be suitable for treatment of anti-cholinergic intoxication.

However, this stands in contrast to the claimed invention. The present invention provides that non-anticholinergically induced deliria either improve following the

administration of cholinomimetic drugs called acetylcholinesterase-inhibitors, or can be effectively prevented by the use of acetylcholinesterase-inhibitors. This has never been described before. Indeed, acetylcholinesterase-inhibitors (donepezil, rivastigmine, galantamine) have not been used before to treat non-anticholinergic delirium.

Indeed, the state-of-the-art teaches treating this complication with neuroleptics like haloperidol. Moreover, most articles in peer-reviewed journals do not mention the possible benefit of physostigmine in the anticholinergic type of delirium. For example, while Parikh SS et al (Postoperative Delirum in the Elderly. Anaesth Analg 1995;80: 1223-32) describe "an association between postoperative confusion and anticholinergic drug activity .." (p. 1224), they do not mention physostigmine nor other cholinomimetic drugs in the management of delirium (p. 1229).

Rather, the state-of-the-art teaches the use of drugs like neuroleptics, benzodiazepines and vitamins. The Examiner's attention is also directed to Dyer CB et al (Postoperative Delirium. Arch Int Med 1995;155:461-465), wherein it is not even mentioned that cholinomimetics may be used as possible therapeutics in delirium.

Applicant believes the treatment of delayed Post Anaesthetic Arousal Phase helps demonstrate the benefits of the present invention. On discontinuation of anaesthesia one should aim to produce, as soon as possible, a conscious and cooperative

patient. "Anticholinergic drugs are often responsible for disturbed recovery from anaesthesia and "central anticholinergic syndrome" can be applied when this etiology is proved "(cited from O'Keeffe ST & Chonchubhair AN (1994).

The term "central anticholinergic syndrome" describes the psychopathology and peripheral anticholinergic signs in patients who do not properly awake from general anaesthesia in an emergence situation. It has also been called "emergence delirium" (O'Keeffe ST & Chonchubhair AN, 1994), postanaesthetic depression, or postoperative somnolence (Rupreht J & Dworacek B. Syndrome Anticholinergique Central en Période Postopératoire. Ann Fr Aesth Réanim 1990;9:295-304). "Emergence delirium" is nowadays a diagnosis for comatose or excited states of children after general anaesthesia.

"Central anticholinergic syndromes" or "emergence delirium" are not "acute confusional states (i.e.,deliria)" in the sense of the terminology of the DSM-IV or ICD-10, but develop out of a state of unconsciousness immediately after anaesthesia. Patients who recover only slowly from general anaesthesia may

suffer from anticholinergic toxicity because they recently received anticholinergic drugs and may respond to physostigmine.

Because anticholinergics are still frequently used in general anaesthesia, some anaesthesiologists even recommend the administration of physostigmine in these patients before an exact diagnosis is made, i.e. before hypoxia, hypercapnia, hyperthermia, hypothermia, urea and electrolyte, and neurological disturbances are excluded (Rupreht J & Dworacek B., Central Anticholinergic Syndrome in Anaesthetic Practice. Acta Anaesthesiologica Belgica 1976;27:45-60). Rupreht et al. suggest that physostigmine can be included in the armamentarium of an anesthesist to combat anticholinergic poisoning. This does not apply to postoperative delirium which develops after a "lucid period of any duration" (cited from O'Keeffe ST & Chonchubhair AN, 1994), which is the focus of the pending application.

Rupreht J & Dworacek B (1990) and other anaesthesiologists who have written on the subject of central anticholinergic syndrome in a post-anaesthesia arousal phase, recommend the administration of physostigmine exclusively for the treatment of post-anaesthetic anticholinergic intoxication, and not for the treatment of any non-anticholinergic postoperative delirium diagnosed after post-anaesthetic arousal.

Indeed, they clearly define two different types of problems during the post-anaesthesia arousal phase. Rupreht et al. state, "Nevertheless, among the anesthetic agents currently

used, some may disturb the arousal phase due to their anticholinergic effects on the central nervous system. These effects, which make up the central anticholinergic syndrome (CAS), are different from other arousal phase problems and may be corrected by a centrally active anticholinesterase agent for crossing the blood-brain barrier, such as physostigmine" (see introduction c J & Dworacek B, 1990).

Thus, no existing literature can be found that recommends the application of physostigmine in a patient who does not receive anticholinergics or suffers from a non-anticholinergic state of delirium.

As a result, applicants believe that Rupreht et al. fail to anticipate or render obvious the claimed invention.

As to the rejection of ENZ 5,602,176 in view of OSHIRO et al. 5,556,857, this rejection is also respectfully traversed.

ENZ is directed to a cholinesterase inhibitor phenyl carbamate. ENZ describes an action mechanism together with the pharmakinetics and dynamics of the compound. ENZ teaches that the phenyl carbamate compounds are useful for the treatment of senile dementia, Alzheimer's disease, Huntington's chorea, tardive dyskinesias, hyperkinesias, mania, acute confusion disorders, Down's syndrome and Friedrich ataxia. As a result, it is respectfully submitted that the ENZ patent is directed to indications of these anticholinergic related disorders (See column 10, item 6).

However, the present invention relates to the administration of acetylcholine esterase inhibitors for treating deliria caused neither by anticholinergic intoxication nor by degeneration of the cholinergic system. Thus, it is respectfully submitted that ENZ fails to disclose or suggest the claimed invention.

In an effort to remedy the deficiencies of ENZ, the Official Action combines OSHIRO et al. However, it is respectfully submitted that one of ordinary skill in the art would lack the motivation to combine these publications. Moreover, even if one was to combine these references, it is respectfully submitted that the combination would fail to suggest the claimed invention.

OSHIRO et al. relate to a disturbance-of-consciousness improving agent which is highly effective and a quick remedy. It is respectfully submitted that the concept of consciousness discussed by OSHIRO et al. is taken out of context by the Official Action.

It is believed that this publication is directed to the treatment of disorientation. At column 1, line 62 to column 2, OSHIRO et al. note that "Confusion" and "delirium" are described as late sequelae or problems of a chronic stage after coma. However, the present invention relates to acutely occurring confusion and not coma states or post-coma sequelae. Applicants respectfully submit that all current diagnosis systems call

acutely occurring states with fluctuating consciousness delirium (See DSM-IV APA, 1994).

OSHIRO et al. relate to patients with awareness disorders. Therefore, OSHIRO et al. do not relate to patients with fluctuating consciousness disorders nor to acute disorders. DSM-IV states that an acute disorder must occur within a few hours to a maximum of 24 hours after an event that damages brain function. This contradiction can also be illustrated on other details of the theoretical description set forth in OSHIRO et al. In column 2, lines 13-43, it is first described that acetylcholine improves "disturbances of consciousness" - therefore awareness. Then it is described that dopaminergic stimulants such as methamphetamine act likewise. However, these substances may not be given in conjunction with the claimed invention because they may demonstrably intensify the symptoms of "acute confusion" or delirium. For example, these compounds are known to promote hallucinations and delusions. Thus, it is respectfully submitted that the proposed combination not only fails to disclose or suggest the claimed invention, but that it would actually lead one of ordinary skill in the art away from the claimed invention.

Moreover, OSHIRO et al. describe that dopamine receptor-blocking substances such as haloperidol prolong the disorders of consciousness intended here. It is respectfully submitted that this demonstrates that the OSHIRO et al.

publication relates to treatment of chronic sequelae of comatous states (coma, precoma, stupor, somnolence), especially after head trauma. It cannot be taken from OSHIRO et al. that different neurotransmitters, including acetylcholine, are important for the "level of consciousness", and that other disorders of consciousness, respond likewise to cholinergic substances, especially when they are not the result of anticholinergic substance intoxication.

Thus, in view of the above, applicants believe that the proposed combination of ENZ in view of OSHIRO et al. fails to render obvious the claimed invention.

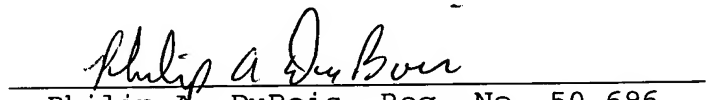
Thus, in view of the above, applicants believe that this application is in condition for allowance, with claims 7-16, as presented. Such action is accordingly respectfully requested.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any

overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON



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